## Phylogeny

• Ser/Thr ePK superfamily → CAMK group → CaMKI subfamily → CaMKIγ/CAMK1G isoform (unknownauthors2012evaluationofprotein pages 18-22).  
• Paralogous human genes within the subfamily: CAMK1 (α), PNCK/CAMK1B (β), CAMK1D (δ), CAMK1G (γ) (brzozowski2019themultifunctionalcalciumcalmodulin pages 1-4).  
• Representative orthologs with experimentally confirmed coding sequences  
– Homo sapiens (Q96NX5)  
– Mus musculus (Q9D8E9)  
– Rattus norvegicus (P56397)  
– Danio rerio (Q6PIZ5)  
– Drosophila melanogaster (Q9W298) (ohmae2006molecularidentificationand pages 4-5).  
• Phylogenetic trees based on the kinase domain place CaMKIγ together with the other CaMKI isoforms and clearly separate the clade from CaMKII and CaMKIV branches (ohmae2006molecularidentificationand pages 5-6).

## Reaction Catalyzed

ATP + [protein]-Ser/Thr → ADP + [protein]-O-phospho-Ser/Thr (unknownauthors2023ascreeningfor pages 133-137).

## Cofactor Requirements

Catalytic phosphotransfer requires Mg²⁺; Mn²⁺ can substitute in standard CaMKI family assays (brzozowski2019themultifunctionalcalciumcalmodulin pages 19-21).

## Substrate Specificity

• Validated substrates  
– CREB1 transcription factor (Ser¹³³) (ohmae2006molecularidentificationand pages 1-1)  
– LIMK1 within the CaMKI–LIMK–cofilin pathway (unknownauthors2012evaluationofprotein pages 42-48).  
• A family-wide preference for basic residues N-terminal to the phospho-acceptor (Arg/Lys-X-X-Ser/Thr) is inferred from CaMKI biochemical studies; no CaMKIγ-specific motif mapping is reported in the supplied sources (unknownauthors2012evaluationofprotein pages 54-58).

## Structure

• Domain organisation  
– Residues 1-279: catalytic kinase domain (small β-lobe + large α-lobe) containing VAIK, HRD, DFG and APE motifs (unknownauthors2012evaluationofprotein pages 54-58).  
– Residues 280-322: regulatory domain composed of αR1/αR2 helices that form the autoinhibitory domain (AID) overlapping the calmodulin-binding domain (CBD) (unknownauthors2012evaluationofprotein pages 36-42).  
– Residues 323-414: unique C-terminal extension; last four residues form a CAAX prenylation motif for membrane anchoring (unknownauthors2012evaluationofprotein pages 36-42).

• 3-D data  
– Homology crystal structures: CaMKIα (PDB 1MRW) and CaMKIδ (PDB 4FG8) show the conserved bilobal fold and AID helix packing (unknownauthors2012evaluationofprotein pages 245-254).  
– AlphaFold full-length model AF-Q96NX5-F1 covers flexible regions including the CAAX-tail (unknownauthors2012evaluationofprotein pages 245-254).

• Catalytic/regulatory features  
– Activation loop Thr¹⁷⁷ (numbering by homology to CaMKIδ) is the CaMKK phosphorylation site (takemoto‐kimura2017calmodulinkinasesessential pages 4-6).  
– Hydrophobic regulatory and catalytic spines align in the active conformation; αC-helix mobility modulates spine completion as observed in CaMKI family NMR studies (unknownauthors2012evaluationofprotein pages 178-187).

## Regulation

• Phosphorylation  
– Thr¹⁷⁷ in the activation loop phosphorylated by CaMKK1 and CaMKK2 increases catalytic activity (takemoto‐kimura2017calmodulinkinasesessential pages 4-6).  
– Dephosphorylation by PP2A and PP2B lowers activity (takemoto‐kimura2017calmodulinkinasesessential pages 16-18).

• Ca²⁺/calmodulin binding  
– Ca²⁺/CaM binding to the CBD displaces the AID from the catalytic cleft, relieving autoinhibition (unknownauthors2012evaluationofprotein pages 36-42).

• Lipid modification  
– Prenylation of the CAAX cysteine (C-terminal four residues) is required for Golgi/plasma-membrane localisation; mutation or prenylation blockade redistributes the kinase to the cytosol (unknownauthors2012evaluationofprotein pages 36-42).

## Function

• Expression  
– High basal mRNA and protein levels in limbic brain regions: central amygdala, bed nucleus of the stria terminalis, ventromedial hypothalamus, hippocampus and medial frontal cortex (piechota2022glucocorticoidregulatedkinasecamkiγ pages 4-6).  
– Lower expression in peripheral organs; neuronal enrichment confirmed by in-situ analyses (unknownauthors2012evaluationofprotein pages 42-48).  
– Glucocorticoids and acute stress strongly up-regulate transcription in the central amygdala (piechota2022glucocorticoidregulatedkinasecamkiγ pages 4-6).

• Upstream regulators  
– Ca²⁺/calmodulin (direct) and CaMKK1/2 (phosphorylation) (takemoto‐kimura2017calmodulinkinasesessential pages 4-6).

• Downstream effectors  
– CREB1 phosphorylation links CaMKIγ to Ca²⁺-dependent gene expression (ohmae2006molecularidentificationand pages 1-1).  
– Activation of LIMK1 and ERK pathways drives actin polymerisation and dendrite development (unknownauthors2012evaluationofprotein pages 42-48).

• Physiological roles  
– Modulates anxiety-like behaviour and conditioned fear; Camk1g-knockdown mice display increased freezing and anxiety phenotypes (piechota2022glucocorticoidregulatedkinasecamkiγ pages 4-6).  
– Promotes neuronal morphogenesis, including dendritic arborisation in response to activity (unknownauthors2012evaluationofprotein pages 42-48).

## Other Comments

• Elevated CAMK1G expression correlates with poor prognosis in clear-cell renal carcinoma (brzozowski2019themultifunctionalcalciumcalmodulin pages 23-24).  
• CAMK1G co-expression modules are enriched in schizophrenia transcriptomic datasets (piechota2022glucocorticoidregulatedkinasecamkiγ pages 4-6).

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